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08/478 748

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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08/478,748 06/07/95 WALDMANN

T 2026-4003US3

EXAMINER  
GAMBEL, P

18M1/0904

NATIONAL INSTITUTES OF HEALTH  
PATENT BRANCH  
OFFICE OF TECHNOLOGY TRANSFER  
BOX OTT  
BETHESDA MD 20892

ART UNIT PAPER NUMBER

DATE MAILED: 1816

7

09/04/96

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### OFFICE ACTION SUMMARY

Responsive to communication(s) filed on \_\_\_\_\_

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1-25 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

Notice of Reference Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

**DETAILED ACTION**

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1816.
2. The filing date of the instant claims is deemed to be the filing date of the instant application, i.e. 6/7/95, as the parent applications do not support the broader claims of the instant application, including the claimed dosage ranges and radionuclide activity (e.g. 2-100 mg, 5-15mCi, second treatment of 100 mg unconjugated anti-Tac, 10-100 µg/kg), the targeted diseases (claims 7-12), the addition of G-CSF (claim 15), anti-Tac(Fv)-PE/anti-Tac-PE38 (claims 22-23) and anti-Tac preparation (versus antibody, claims 24-25).
3. The specification on page 1 should be amended to reflect the status of the various parent applications and the relationship with the instant application.
4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including the Tac-specificity.
5. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).
6. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.  
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).
7. The application is required to be reviewed and all spelling, TRADEMARKS and like errors corrected.
8. Claims 24-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
  - A) Claims 24-25 are indefinite in the recitation of "anti-Tac preparation" because "preparation" is ambiguous and unclear. Applicant should amend the claims to recite "antibody" or "monoclonal antibody" to correspond with the disclosed invention.

B) Claim 25 is indefinite in the recitation of "wherein the effective dosage .... is provided" because it is not clear whether the pharmaceutical composition comprises this dosage range or whether the dosage range is intended for method claims and the pharmaceutical composition can comprise dosage ranges outside that recited.

The amendments must be supported by the specification so as not to add any new matter.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claim 24 is rejected under 35 U.S.C. § 102(b) as being anticipated by Kozak et al. (PNAS, 1986). Kozak et al. teaches <sup>212</sup>Bismuth-labeled anti-Tac monoclonal antibody. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention.

12. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Ann. Oncol., 1994; 1449, #1) (see entire document). Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with <sup>90</sup>Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease encompassed by the claimed methods. Waldmann is silent about effective dosages per se. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977) and In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

13. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Important Adv. Oncol., 1994) (see entire document). Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with <sup>90</sup>Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease encompassed by the claimed methods. Waldmann is silent about effective dosages per se. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977) and In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

14. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Leukemia, 1993) (see entire document). Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with <sup>90</sup>Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease encompassed by the claimed methods. Waldmann is silent about effective dosages per se. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was

made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977) and In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

15. Claims 1-14 and 16-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993). The instant claims are drawn to using conjugated-anti-Tac antibodies in the treatment of various diseases.

The Waldmann references all review the use of <sup>90</sup>Y-labelled and cytotoxin-conjugated anti-Tac antibodies in the treatment of the leukemias, lymphomas, autoimmune dysfunctions and allograft incompatibility encompassed by the claimed invention (see entire documents). These references differ by not disclosing the dosage ranges per se, even though said ranges are taught in the references disclosed in these review articles.

For example, Hakimi et al. and Waldmann teach the use of dosage ranges and radionuclide activity ranges encompassed by the claimed methods and compositions (see entire document).

Similarly, Kreitman et al. teach the dosage ranges and antibody forms of immunotoxin-conjugated anti-Tac antibodies (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to select radiolabeled-conjugated and immunotoxin-conjugated anti-Tac antibodies to target Tac-expressing cells in various disorders in the dosage and activity ranges encompassed by the claimed methods. These limitations were known and practiced or would have been met based upon the need of a particular patient and their disease state at the time the invention was made. The references teach that both conjugated and unconjugated anti-Tac antibodies are effective in various therapeutic modalities. Due to their common known purpose and the known toxicity of conjugated anti-Tac antibodies, it would have been obvious to use conjugated anti-Tac antibodies followed by unconjugated anti-Tac antibodies in therapeutic regimen to eliminate or reduce undesirable Tac-expressing cells.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) as applied to claims 1-14 and 16-25 above and in further view of Parenteau et al. (Transplantation et al.) Claim 15 is drawn to the use of G-CSF in combination with anti-Tac therapy.

Parenteau et al. teach the use G-CSF in the treatment of anti-Tac treated recipients undergoing allograft transplantation (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to select radiolabeled-conjugated and immunotoxin-conjugated anti-Tac antibodies to target Tac-expressing cells in various disorders in the dosage and activity ranges encompassed by the claimed methods. These limitations were known and practiced or would have been met based upon the need of a particular patient and their disease state at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. In the event that applicant intends that the claimed pharmaceutical compositions (claims 24-25) are drawn to anti-Tac antibody pharmaceutical compositions which find written support in parent applications, the following rejection of record in copending USSN 07/879,056 is set forth herein.

Claims 25-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Kozak et al. (PNAS, 1986) or Diamantstein et al. (Immunol. Rev., 1986) in view of Order et al. (Int. J. Radiat. Oncol. Biol. Phys., 1986) or Wessels et al. (Med. Phys., 1984). The instant claims are drawn to pharmaceutical compositions comprising anti-Tac antibodies or 90Y-conjugated anti-Tac antibodies.

Kozak et al. teach anti-Tac monoclonal antibody conjugated with Bismuth-212, an  $\alpha$ -particle emitting radionuclide, as a radioimmunotherapeutic modality (see entire document). Kozak et al. teach that  $^{212}\text{Bismuth}$ -conjugated anti-Tac antibody can serve as a radioimmunotherapeutic reagents to eliminate unwanted Tac expressing T cells in patients with adult T cell leukemia, autoimmunity and organ transplantation (page 478, column 2). Also, Kozak et al. teach that there are numerous  $\alpha$ -,  $\beta$ -,  $\gamma$ -emitting radioisotopes that are suitable for different forms of therapy (page 477, column 1).

Diamantstein et al. teach anti-interleukin-2 receptor antibodies (anti-Tac) as a new approach to a selective immunosuppressive therapy in humans of undesired immune responses, such as graft-versus-host reactions, allograft rejection, and autoimmunity (see entire document, particularly pages 17-24). Diamantstein et al. exemplify such immunosuppression with anti-interleukin-2 receptor antibodies in various models of allogeneic transplantation disease in mice and rats.

Both references disclose the art-known observations that activated T cells and certain leukemic T cells express interleukin-2 receptors but resting or precursor T cells do not. Kozak et al. and Diamantstein et al. do not teach immunotherapy with anti-Tac monoclonal antibody conjugated with a  $\beta$ -emitting radionuclide.

Order et al. exemplify  $^{90}\text{Yttrium}$  conjugated antiferritin antibodies for the treatment of hepatocellular cancer (see entire document). Order et al. teach that the advantages of  $^{90}\text{Yttrium}$  include a greater potential tumor dose rate and total tumor dose, no inpatient requirements, the ability to treat pediatric patients as well as a known method for antibody linkage (page 277, column 1, paragraph 2).

Wessels et al. teach  $^{90}\text{Yttrium}$  has been determined to be among the best therapy radiolabels since it possesses sufficiently long half life necessary for tumor localization, little or no gamma radiation, intermediate beta energy, stable daughter products, and has a reasonable chance to form a stable chelate with an antibody system (see entire document).

One of ordinary skill in the art at the time the invention was made would have made been motivated to make anti-Tac monoclonal antibodies conjugated to a  $\beta$ -emmitting isotope such as  $^{90}\text{Yttrium}$  as a better radioimmunotherapeutic reagent for the reasons cited above. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references to make  $^{90}\text{Yttrium}$  conjugated anti-

Tac antibodies as a highly effective radiopharmaceutical reagent to eliminate unwanted Tac positive cells observed in a number of T-cell mediated disorders in humans. These disorders would include T cell leukemia, autoimmunity and transplantation all of which were well-known in the art at the time the invention was made to involve Tac positive cells. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because anti-Tac monoclonal antibodies including those conjugated were known to suppress responses by Tac positive cells including human Tac positive cells and <sup>90</sup>Yttrium antiferritin antibodies were shown to be safe and effective in tumor regression.

18. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (1-5, 13, 22 and 28) of copending application Serial No. 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993). Although the conflicting claims are not identical, they are not patentably distinct from each other because each composition is drawn to the similar conjugated anti-Tac antibodies treating the same or similar diseases. The Waldmann review references all teach the use of radiolabel and immunotoxin conjugated anti-Tac antibodies in therapeutic modalities associated with the reduction or elimination of Tac-expressing cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-25 are directed to an invention not patentably distinct from claims (1-5, 13, 22 and 28) of commonly assigned USSN 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993). Although the conflicting claims are not identical, they are not patentably distinct from each other because each composition is drawn to the similar conjugated anti-Tac antibodies treating the same or similar diseases. The Waldmann review references all teach the use of radiolabel and immunotoxin conjugated anti-Tac antibodies in therapeutic modalities associated with the reduction or elimination of Tac-expressing cells.

Commonly assigned USSN 07/879,056, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

21. No claim is allowed.

22. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Serial No. 08/478748  
Art Unit 1816

-10-

Phillip Gambel, Ph.D.  
Patent Examiner  
Group 1800  
September 3, 1996

A handwritten signature in black ink, appearing to read "Phillip Gambel". The signature is fluid and cursive, with some loops and variations in letter form.